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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/151,409	09/10/98	DALE J	481112.410

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HM12/0815

EXAMINER	
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ART UNIT	PAPER NUMBER
1645	25

DATE MAILED: 08/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/151,409	Dale et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 30, 2001*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12-48* is/are pending in the application.

4a) Of the above, claim(s) *48* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12-47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *Part of 19*.

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1) The request filed on 03/02/2001 (paper no. 20) for a Continued Prosecution Application (C.P.A) under 37 C.F.R 1.53(d) based on parent Application, SN 09/151,409, is acceptable and a C.P.A has been established. An action on the C.P.A follows.

Applicant's Amendments

2) Acknowledgment is made of Applicant's preliminary amendment filed 03/12/01 (paper no. 21) and the amendment filed 04/30/01 (paper no. 24). With the preliminary amendment, Applicant has introduced amendments to the specification. These amendments to the specification have not been entered, since the page and/or line numbers where Applicant has requested the amendments appear to be incorrect.

Election

3) Acknowledgment is made of Applicants' election filed 04/30/01 (paper no. 24), of invention I, claims 12-47, in response to the restriction requirement mailed 03/28/01 (paper no. 23). Since Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P § 818.03(a)). The restriction requirement is hereby made FINAL.

Status of Claims

4) Claims 49-53 have been canceled via the amendment filed 04/30/01.

Claims 1-48 are pending.

Claim 48 has been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

The elected claims 12-47 are under examination. An Action on the Merits for these claims is issued.

Information Disclosure Statement

5) It appears that page "5 of 8" of the information disclosure statement filed 11/05/99 (paper no. 12) was not considered by the previous Examiner of record. The information cited on this page of the IDS has now been considered and a copy of the initialed page has been provided to

Applicant as an attachment to this Office Action (paper no. 25).

Prior Citation of Title 35 Sections

6) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

7) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Priority

8) The instant application claims domestic priority to application SN 60/058,635 filed 09/12/97.

Rejection(s) Moot

9) The rejection of claims 1, 5 and 9-11 maintained in paragraph 4 of the Office Action mailed 02/16/00 (paper no. 15) under 35 U.S.C. § 102(b) as being anticipated by Dale *et al.* (*J. Immunol.* 151: 2188-2194, 1993), or Dale *et al.* (*Vaccine* 14: 944-948, July 1996), is moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 5 and 6 maintained in paragraph 5 of the Office Action mailed 02/16/00 (paper no. 15) under 35 U.S.C. § 102(b) as being anticipated by Dale *et al.* (*J. Exp. Med* 163: 1191-1202, 1986), is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 5 and 7 maintained in paragraph 6 of the Office Action mailed 02/16/00 (paper no. 15) under 35 U.S.C. § 102(b) as being anticipated by Beachey *et al.* (*J. Immunol.* 136: 2287-2292, 1986), is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 1 and 2 maintained in paragraph 7 of the Office Action mailed 02/16/00 (paper no. 15) under 35 U.S.C. § 103(a) as being unpatentable over Dale *et al.* (*J. Exp. Med* 163: 1191-1202, 1986) and Dale *et al.* (*J. Immunol.* 151: 2188-2194, 1993), is moot in light of Applicants' cancellation of the claims.

13) The rejection of claims 1 and 3 maintained in paragraph 8 of the Office Action mailed 02/16/00 (paper no. 15) under 35 U.S.C. § 103(a) as being unpatentable over Beachey *et al.* (*J.*

Immunol. 136: 2287-2292, 1986) and Dale *et al.* (*J. Immunol.* 151: 2188-2194, 1993), is moot in light of Applicants' cancellation of the claims.

14) The rejection of claims 1 and 4 maintained in paragraph 9 of the Office Action mailed 02/16/00 (paper no. 15) under 35 U.S.C. § 103(a) as being unpatentable over Dale *et al.* (*J. Immunol.* 151: 2188-2194, 1993) and Beall (*J. Clin. Microbiol.* 34: 953-958, 1996), is moot in light of Applicants' cancellation of the claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

15) Claims 16, 18, 20, 22, 24, 26, 37, 39, 41, 43, 45 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims recite a recombinant fusion polypeptide comprising an immunogenic portion which comprises "six" immunogenic peptides of serotype 1, or serotype 4, or serotype 5, or serotype 6, or serotype 12. Applicants point to page 7, lines 25 through page 8, line 18; Examples 1 and 3-7; page 2, lines 17-30; and page 12, line 14 through page 13, line 3 as containing support for these new claims. However, there appears to be no support in these parts of the instant specification for a fusion polypeptide that contains "six" immunogenic peptides from the same serotype, i.e., 1, 4, 5, 6 or 12. Example 1 describes a hexavalent fusion polypeptide comprising immunogenic peptides from types 24, 5, 6, 19, 1 and 3. Therefore, the above-identified new limitation(s) in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claims.

16) Claims 13 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims recite that the C-terminal "peptide" is a reiteration of at least one of the immunogenic peptides. Applicants point to page 7, lines 25 through page 8, line 18; Examples 1 and 3-7; page 2, lines 17-30; and page 12, line 14 through page 13, line 3 as containing support for these new claims. The specification on page 8, lines 16-20 appears to provide support for a 'reiterated immunogenic polypeptide" that may be included at the end of the vaccine. However, there appears to be no support for a reiterated 'peptide' as recited in instant claims. Therefore, the above-identified new limitation(s) in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claims.

Rejection(s) under 35 U.S.C. § 102

17) Claims 12-15, 17, 19, 21, 23, 25, 27-31, 36, 38, 40, 42, 44 and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dale *et al.* (WO 94/06421 - Applicant's IDS) ('421).

Dale *et al.* ('421) disclose a recombinant fusion or hybrid polypeptide comprising at least two immunogenic peptides comprising at least ten amino acids capable of eliciting an immune response against group A streptococcal infections. A vaccine comprising a recombinant multivalent hybrid M protein vaccine is taught for use against multiple serotypes of group A streptococci. The vaccine contains epitopes or antigenic determinants (i.e., immunogenic peptides) that evoke opsonic antibodies against multiple serotypes of group A streptococci (see page 8, last paragraph), including serotypes 1, 3, 5, 6, 14, 18, 24, 27, 29 or others (see page 9, third full paragraph; see claims, especially claims 1-16). The hybrid M proteins include amino acids of the amino termini of the M proteins, i.e., M24, M5, M6 and M19 and amino acids of the carboxy-terminus (i.e., a C-terminal peptide) of type 5M protein. The vaccine raises type-specific opsonic antibodies against all of the related M fractions, cross-protective mucosal immune

responses against two or more of these and cellular immunity (see page 10, last paragraph; page 12; and the Figures 8 and 11 descriptions). A therapeutic composition comprising a pharmaceutically acceptable carrier and recombinant multivalent hybrid M proteins is taught. The hybrid polypeptide may be injected to a mammal in an appropriate biologically acceptable diluent or in complete or incomplete Freund's adjuvant (see page 11, second paragraph; page 36, third full paragraph; and page 37, first full paragraph). The immunogenic portions contain 15 amino acid units (see page 13, lines 1-2). A recombinant octavalent hybrid protein that contains a non-rheumatogenic serotype of M12 streptococcus is taught (see the description for Figure 13). The polyvalent or hybrid M proteins contained in phosphate buffered saline and complete Freund's adjuvant are used to immunize rabbits. The use of a mixture or cocktail of such hybrid proteins is taught (see page 23, middle paragraph). Dale *et al.* disclose recombinant hybrid polypeptides comprising repeated (i.e., reiterated) amino acid fractions of different serotypes of group A streptococci, for example, M24-M24-M24-M5-M5-M5-M6-M6-M6-M19-M19-M19 multivalent hybrid (see page 27, fourth full paragraph). A hybrid construct containing tetravalent M24-M25-M6-M19 peptides with the carboxy terminal half of M5 joined therein, is disclosed (see page 28, last paragraph). A method of combining the multivalent vaccine with that of a carboxy terminal of one of the M protein serotypes is taught (see page 29, first full paragraph). The carboxy terminal of M24, M19 and M6 (i.e., from another pathogen) may be used in place of the carboxy terminal of M5 as long as the carboxyl terminal does not generate tissue-crossreactive antibodies. Such a construct, not only generates opsonic antibodies against the carboxy terminal portion of the molecule, but thus can serve as a vaccine or as an effective therapeutic or prophylactic agent (see page 29, second and third full paragraphs). Instead of using the entire carboxyl terminal of anyone of the M serotypes, it may be advantageous to use only a few amino acids of the C repeats of the carboxyl terminal of a particular serotype of group A streptococcus. The carboxyl terminal or the amino acids constituting one or more C-repeats used in the construct need not be one of the same serotype(s) as that which constitutes the amino terminal portion of the construct. Such a vaccine would provide cellular immune responses than the opsonic response and concurrently provide type-specific immunity (see page 29, fourth paragraph; and page 31, fifth full paragraph). A multivalent vaccine comprising M19, M6, M5 and M24 fragments that are 35, 35, 58 and 113

amino acid residues-long (see page 30, lines 11-13) is taught. Dale *et al.* ('421) teach vaccines that include amino acid subunits of any or all of the 1 through 80 different serotypes known or to be discovered (see page 34, second paragraph).

Claims 12-15, 17, 19, 21, 23, 25, 27-31, 36, 38, 40, 42, 44 and 46 are anticipated by Dale *et al.* ('421).

Rejection(s) under 35 U.S.C. § 103

18) Claims 27 and 32-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dale *et al.* (WO 94/06421 - Applicant's IDS) ('421) in combination with Pillai *et al.* (US 5,334,379).

The teachings of Dale *et al.* ('421) are described above which do not disclose their composition further comprising a immunomodulatory cofactor, such as, IL-2, IL-4 or IFN-gamma.

However, Pillai *et al.* disclose that cytokines and lymphokines, such as, interferons, IL-2 and IL-4, are the modulators of the immune response, and that these modulators augment proliferation and differentiation of antigen or mitogen stimulated T cells. Cytokines and lymphokines are taught to have adjuvant activity with the capacity to enhance the immune response to an antigen (see column 1, lines 11-39). Pillai *et al.* further teach that cytokines and lymphokines "help evoke a protective immune response against marginally or non-immunogenic conjugated antigens, and bound unconjugated antigens" (see paragraph bridging columns 6 and 7).

It would have *prima facie* been obvious to one skilled in the art at the time the invention was made to add Pillai's IL-2 or IL-4 to Dale's composition comprising the fusion M polypeptide, to produce the composition of the instant invention with a reasonable expectation of success, because Pillai *et al.* explicitly teach that the recited cytokines have immune-enhancing adjuvant activity and the ability to evoke a protective immune response to the antigen present. One skilled in the art would be motivated to produce the instant invention for the expected benefit of producing a fusion M polypeptide vaccine composition having enhanced immunogenicity, since such vaccine compositions are ideally desired in the art of vaccines.

Claims 27 and 32-35 are *prima facie* obvious over the prior art of record.

Objection(s)

19) Claims 1 and 31 are objected to for the following reasons:

(a) Claim 31 is incorrect in the recitation "bacteria is" [Emphasis added]. To be correct, it is suggested that Applicants replace the recitation with --bacterium is--.

(b) Claim 31 is incorrect in the recitation "*V. cholera*". To be correct, it is suggested that Applicants replace the recitation with --*V. cholerae*--.

(c) Claim 1 is confusing and/or incorrect in the recitation "bacteria of the genus *Vibrio*" and "at least one gene from said bacteria" [Emphasis added]. It is suggested that Applicants replace the recitation "bacteria" with --bacterium--.

Remarks

20) Claims 12-47 stand rejected.

21) The prior art made of record and not currently relied upon in any rejection is considered pertinent to Applicants' disclosure:

- Beachey *et al.* (*J. Exp. Med.* 166: 647-656, 1987 - Applicant's IDS) teach a hybrid M protein vaccine of Group A streptococcus comprising immunogenic peptides from types 5, 6 and 24 and a carboxyl-terminal cysteine residue (see entire document).

- Dale *et al.* (US 6,063,386) disclose a hybrid M protein vaccine of Group A streptococcus comprising immunogenic peptides from different types of group A streptococcus and a carboxyl-terminal cysteine residue (see entire document).

- Dale *et al.* (*Vaccine* 14: 944-948, 1996, already of record) teach a recombinant group A streptococcal octavalent hybrid M protein (i.e., a fusion polypeptide) comprising immunogenic and protective peptides each having at least ten amino acids. The peptides are from different group A streptococcal serotypes. The recombinant hybrid polypeptide elicits opsonic antibodies against 6-8 different serotypes of group A streptococci (see abstract; Materials and Methods; Results and page 944). The octavalent vaccine contains carboxy-terminal M18 and M2 subunit fragments, which did not evoke opsonic antibodies (see page 946, right column).

- Dale *et al.* (*J. Immunol.* 151: 2188-2194, 1993, already of record) teach that fusion proteins (i.e., similar to their tetravalent Group A streptococcal M protein fusion proteins)

may be engineered that contain protective epitopes from multiple different organisms (see page 2193, left column, third full paragraph).

- Dale *et al.* (*J. Infect. Dis.* 171: 1038-1041, 1995) (Dale *et al.*,1995) teach a recombinant group A streptococcal M protein fragment fused to the B subunit fragment of *E. coli* labile toxin (see abstract).

22) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

23) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD

S. Devi, Ph.D.
Primary Examiner
August 2001